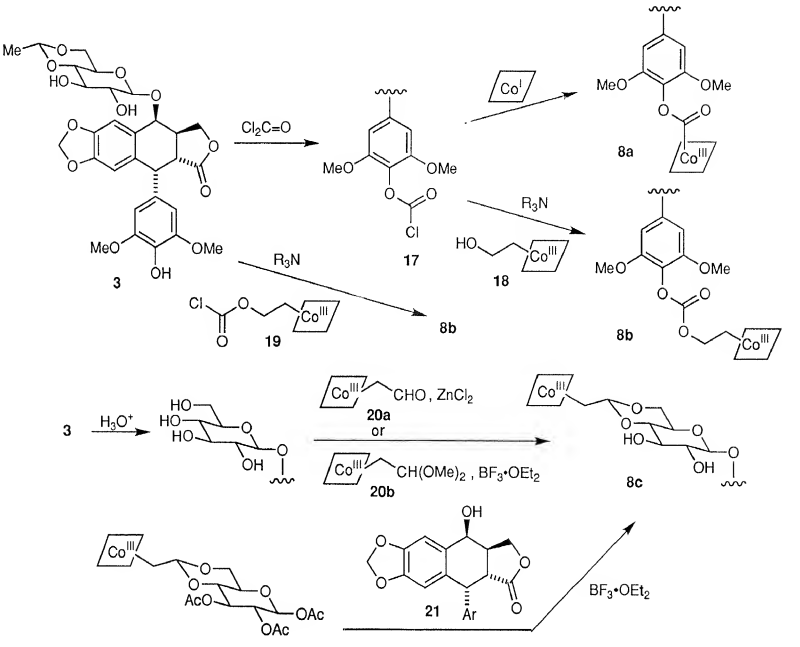
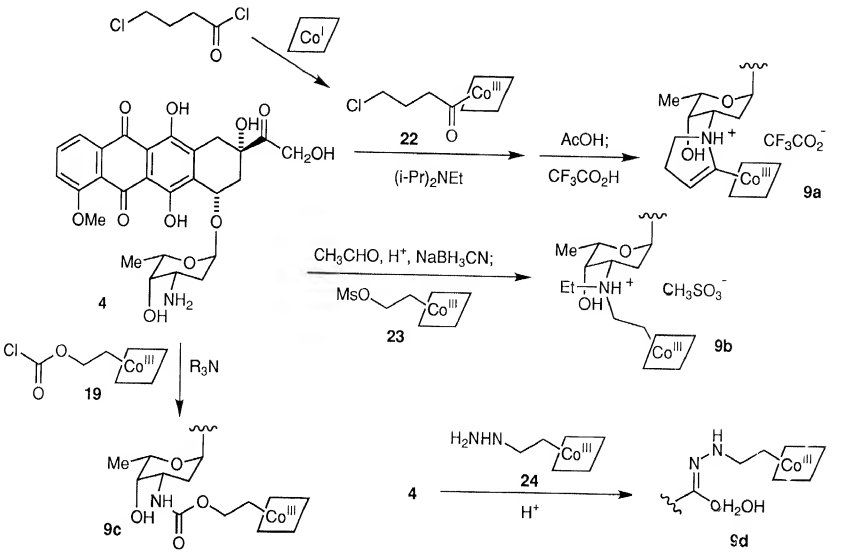


A doxorubicin-containing bioconjugate can be synthesized by the following method. Doxorubicin (**4**) is the most widely used of the anthracycline antibiotics, and is clinically useful against a broad spectrum of solid and hematological tumors. Like etoposide, doxorubicin appears to target topoisomerase II, ultimately leading to growth arrest and nonapoptotic cell death (Fornari et al., 1996; Ling et al., 1996). The clinical usefulness of doxorubicin is limited by nonspecific toxicity, especially cardiotoxicity. Thus, it would appear to be a particularly good candidate for selective delivery. This is confirmed by its frequent use in liposome-based methods (Hu et al., 1996; Longman et al., 1995; Hosada et al., 1995), as part of immunoconjugates (Johnson et al., 1995; Sivam et al., 1995), or in prodrug approaches (Svensson et al., 1995).

Doxorubicin conjugated to cobalamin, Co[SALEN] and other organocobalt complexes according to the following reaction schemes. For the synthesis bioconjugate **9a**, the condensation of the daunosamine amino group with acyl-Co(III) complex **22** is performed. This reaction forms the 2-pyrroline ring in analogy to published routes using 4-iodobutyraldehyde and 5-iodo-2-pentanone.(**9b**) The acyclic tertiary amine derivative **9b** is available from **4** via initial reductive amination with acetaldehyde, then alkylation of the resulting secondary amine with the mesylate **23** derived from **18**. Alternatively, treatment of **4** with chloroformate **19** provides carbamate **9c.** If alternative points of attachment are desired, hydrazone-linked derivatives such as **9d** can be used using simple cobalamin alkyl hydrazides such as **24**, obtainable from **23**. The cleavage of these bioconjugates is shown in the reaction scheme below.


Co^I
22
(i-Pr)2NEt
AcOH;
CF3CO2H
9a
4
CH3CHO, H+, NaBH3CN;
23
9b
19
R3N
9c
24
H+
9d